I. REMARKS

Claim 71 is canceled herein. Applicant reserves the right to pursue the subject matter of claim 71 in continuing prosecution of this or related applications. Furthermore, cancellation of claim 71 is not intended to change the scope of pending claims 1 and 76 from which claim 71 depended.

Claim 81 is amended herein to contain proper antecedent basis. The amendment does not represent new matter.

II. PATENTABILITY ARGUMENTS

A. The Rejections of Claim 71 under 35 U.S.C. § 112, First Paragraph

Claim 71 stands rejected as assertedly lacking adequate written description and enablement. Applicant respectfully traverses the rejections. However, in an effort to expedite prosecution of the remaining pending claims, Applicant cancels claim 71 herein and reserves the right to pursue the subject matter of claim 71 in this or a related application. Nonetheless, cancellation of claim 71 renders the rejections moot.

B. The Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 11-13, 15; 71-83 stand rejected as assertedly being indefinite. In particular, the Examiner contends that the metes and bounds of the terms "compound" in claims 1 and 11 and "oligonucleotide mimetic compound" in claim 76 cannot be determined. Applicant respectfully traverses this contention.

Use of the term "compound" in claims 1 and 11 does not render the claims indefinite. First, the term is used as a generic preamble, *e.g.* compound, apparatus, method, etc., and is not meant as a limitation of the claim. The metes and bounds of the claims are provided by the remaining terms. Second, the term is used throughout the specification and numerous examples of compounds of the invention are provided (see the Detailed Description of the Invention and Examples). Thus, the metes and bounds of claims 1 and 11 are determinable when the limitations of the claims are considered and in light of the specification.

Use of the term "oligonucleotide mimetic compound" does not render claim 76 indefinite. Upon reading the specification, particularly pages 12-22 and the examples, one of ordinary skill in the art would understand the term to mean an oligonucleotide compound

comprising one or more modifications in structure from that of RNA or DNA. Many exemplary modifications are provided. Thus, the metes and bounds of claim 76 are determinable.

Furthermore, claim 81 stands rejected for lacking proper antecedent basis for "the antisense oligonuclotide." Claim 81 is amended herein to contain proper antecedent basis, rendering the rejection to the claim moot.

C. The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 11-13, 15 and 71-83 stand rejected under 35 U.S.C. § 112, first paragraph. The rejection asserts that the subject matter of the claims was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses this assertion.

Claim 1, for example, is directed to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3), wherein said compound specifically hybridizes with said nucleic acid molecule and inhibits the expression of human hormone-sensitive lipase by at least 5% in 80% confluent HepG2 cells in culture at an optimal compound concentration. Indications that the inventors were in possession of the claimed invention at the time of filing can be found throughout the specification. For example, original claim 1 recited compounds 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding hormone-sensitive lipase, wherein said compound hybridizes with and inhibits the expression of hormone-sensitive lipase. Inhibition by at least 5% in 80% confluent HepG2 cells in culture at an optimal compound concentration can be found at least at pages 89 and 90.

Although the scope of claim 1 includes many structural variants, the specification is replete with descriptions and examples of the many variants. The distinguishing features of the many variants within the scope of claim 1 are that they are (1) 8 to 50 nucleobases in length, (2) hybridize with a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3), and (3) inhibit the expression of hormone sensitive lipase by at least 5% in 80% confluent HepG2 cells in culture at an optimal compound concentration. Table 2 alone describes over twenty representative species having the distinguishing features of claim 1. The Office Action provides no reasoning or evidence to support the assertion that one of skill in the art would reasonably conclude that the disclosure fails to provide a representative

number of species to describe the various genera claimed. Thus, given the extensive teachings and descriptions provided within the specification, there is no reason to conclude that the specification does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

D. The Rejection under 35 U.S.C. § 102(a)

Claims 1, 2, 4-8, 11-15, and 72-81 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Mitchell *et al.* ("Mitchell"). Applicant respectfully traverses the rejection. In the Response of May 14, 2003, Applicant put forth several arguments as to why Mitchell does not anticipate the present claims. The current rejection does not address those arguments, which are summarized below. Applicant respectfully requests reconsideration of the arguments.

Mitchell does not disclose a single antisense molecule. Mitchell merely discloses a sequence of a gene and suggests antisense technology as a method of inhibiting expression of the gene. Even if Mitchell could be said to disclose antisense molecules, it does not disclose compounds **8 to 50** nucleobases in length that specifically hybridize with and inhibit the expression of human hsl (and methods using such compounds (claim 15)). Although Mitchell states antisense oligonucleotides may comprise about 5 or more nucleotide units, no specific examples falling within the claimed range of 8 to 50 nucleobases are disclosed by Mitchell. According to MPEP § 2131.03, "In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with 'sufficient specificity to constitute an anticipation under the statute.'" Applicant respectfully submits that a reference disclosing a gene sequence and wishing for antisense molecules greater than 5 nucleotide units cannot be said to disclose, with "sufficient specificity to constitute an anticipation," compounds 8 to 50 nucleobases in length that hybridize and inhibit the expression of hsl. Moreover, Mitchell does not disclose compounds that inhibits expression of hsl in the HepG2 assay to the extent presently claimed.

E. The Rejections under 35 U.S.C. § 102(b)

Claims 1, 2, 11, and 72-75 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Holst *et al.* and by Langin *et al.* Applicants respectfully traverse the rejection. In the Response of May 14, 2003, Applicant put forth several arguments as to why Mitchell

does not anticipate the present claims. The current rejection does not address those arguments, which are summarized below. Applicant respectfully requests reconsideration of the arguments.

The rejected claims specify a percent inhibition as measured in a specific assaying method or contain at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding human hormone-sensitive lipase (claim 11). As demonstrated in Table 2 (pages 89 and 90), not all molecules that hybridize with a nucleic acid molecule encoding human hormone-sensitive lipase meet the functional language of the claims. Neither of the cited references disclose, and the Examiner provides no rationale or evidence showing, that the primer disclosed therein inhibits expression of hsl in the HepG2 assay, which is a functional limitation of the claims, or contains at least an 8-nucleobase portion of an active site. Because the references cited against the pending claims fail to teach each and every limitation of the claims, the cited references cannot anticipate the subject matter of the pending claims. The rejections under 35 U.S.C. § 102(b) should be withdrawn.

F. The Rejection under 35 U.S.C. § 103

Claims 1, 2, and 4-15 and 72-83 stand rejected as allegedly unpatentable over Mitchell, Holst, and Langin in view of Milner, Baracchini *et al.*, and Wright. Applicant respectfully traverses the rejection. As discussed above, the primary references do not disclose any compound 8 to 50 nucleobases in length that specifically hybridize with and inhibit expression of hsl, particularly to the extent in the HepG2 assay presently claimed. The teachings of the cited secondary references do not overcome this deficiency. Thus, the rejection fails to put forth a *prima facie* case of obviousness.

The rejection states that Milner discloses a general method to design and assess antisense inhibition of a known gene target *in vitro*. Milner discloses that not all molecules antisense to a target mRNA can form heteroduplexes with the target mRNA *in vitro*. Milner demonstrates that the ability to form heteroduplexes with the target correlates with the ability to mediate RNase H cleavage of the target *in vitro* and disrupt *in vitro* translation. The assays of Milner are *in vitro* ("test tube"). However, Branch (p. 48-49) teaches that such "test tube" assays are unpredictable. Thus, even if there was some motivation to use the assay of Milner, one of skill in the art would not have a reasonable expectation of success using the assay to create a compound of the present claims.

Regarding the other secondary references, Barracchini targets a completely different gene in a different cell line. Wright discloses antisense inhibition of R1 and R2 components of ribonucleotide reductase in HepG2 cells but does not disclose or suggest that the HepG2 cell line expresses hsl. Combination of these references to arrive at the use of HepG2 cells to screen for antisense inhibitors of hsl can be nothing but improper hindsight reconstruction. Because the rejection fails to make a *prima facie* case of obviousness, the rejection under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. The Examiner is invited to contact the undersigned attorney at the number listed below with any questions of form or substance.

Dated: December 29, 2003

Respectfully submitted,

By _____

Thomas J. Wrona, Ph.D.
Registration No.: 44,410
MARSHALL, GERSTEIN & BORUN
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicant